PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20500490KC	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT**/SG2005/000087	International filing date *(day/month/year)* 18 March 2005	Priority date *(day/month/year)* 22 March 2004

International Patent Classification (IPC) or national classification and IPC

Int. Cl.

A61L 27/44 (2006.01) ***A61L 27/58*** (2006.01)

Applicant

AGENCY FOR SCIENCE, TECHNOLOGY & RESEARCH et al

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of **3** sheets, as follows:
      - [ ] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      - [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[ ]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[ ]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[ ]	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17 January 2006	02 March 2006
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **DAVID GRIFFITHS** Telephone No. (02) 6283 2628

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/SG2005/000087

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (under Rules 12.3(a) and 23.1 (b))

[ ] publication of the international application (under Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages **1 - 7** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* **8 - 10** as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the drawings:

pages **1 - 6** as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages
[ ] the claims, Nos.
[ ] the drawings, sheets/figs
[ ] the sequence listing *(specify)*:
[ ] any table(s) related to the sequence listing *(specify)*:

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

Box No. V **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	**1 - 25**	**YES**
	Claims		**NO**
Inventive step (IS)	Claims	**1 - 25**	**YES**
	Claims		**NO**
Industrial applicability (IA)	Claims	**1 - 25**	**YES**
	Claims		**NO**

2. Citations and explanations (Rule 70.7)

The present invention relates to tissue scaffolds comprising at least two polymers wherein the first polymer is leached by a solvent and all other polymers are either not leached by the solvent or have a lower dissolution rate in the solvent wherein leaching of the first polymer is controlled so that leaching of the first polymer is maximised at the surface of the scaffold and minimised at the core.

The following citations, identified in the international search report, are considered in this report:

D1. EP 1 216 717
D2. WO 1999/011297
D3. WO 2002/030481
D4. WO 2002/051463
D5. WO 2002/060508
D6. US 2002/0138154
D7. US 2002/0183858
D8. US 2003/0114936
D9. Derwent Abstract 2003-607789/57

EP 1 216 717 discloses a biocompatible tissue implant comprising one or more layers of a bioabsorbable polymeric foam having pores with an open cell structure. The tissue implant also includes a preferably bioabsorbable reinforcement component that contributes to both the mechanical and the handling properties of the implant. The citation does not disclose or suggest the present claims.

WO 1999/011297 disclose a fully-biodegradable fibre-reinforced composite adapted for use as a medical implant comprising thermoplastic matrix and fibres characterised by a differential degradation of matrix with respect to fibres. The present claims must be considered novel and inventive over this citation.

WO 2002/030481 discloses a cell-delivery device comprising a controllable, degradable gel phase, meshed within a polymer substrate for use in tissue-engineering. The gel phase comprises a degradable, natural or synthetic polymer and includes a suspension of living cells. The polymer substrate comprises a biocompatible, degradable polymer. The present claims must be considered novel and inventive over this citation

WO 2002/051463 discloses an implantable biodegradable device, useful in repair and/or regeneration of mammalian tissue, that comprises a fibrous matrix constructed from fibres A and B, wherein fibre A biodegrades faster than fibre B. The disclosure can be distinguished from the present claims because they relate to a biodegradation that takes place when the scaffold is in the body; the claims on the other hand, relate to a leaching process in the secondary processing that takes place during the manufacturing process. The present claims are therefore novel and inventive in the light of this citation

continued on a supplemental sheet...

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of:Box V

WO 2002/060508 relates to the preparation of a porous, biodegradable tissue-engineering scaffold or medical implant comprising the steps of mixing a copolymer of polyakylene glycol terephtalate and an aromatic polyester with particles that are soluble in a solvent in which the copolymer essentially does not dissolve, and subjecting the mixture to heat and/or pressure to form the scaffold or implant. The soluble particles may be polymeric, for example poly-(meth)acrylate, and are dissolved by solvent to form a porous scaffold. The citation does not disclose or suggest the invention defined in present claims.

US 2002/0138154 discloses the resorption of a medical implant can be controlled with the use of particles, for example of a water-swellable polymer, embedded in a resorbable bulk material forming the implant. The embedded particles have a different and faster resorption rate than the bioresorbable bulk material. The citation does maximising leaching at the surface while minimising it in the interior and so the present claims must be acknowledged as being novel and inventive over this citation.

US 2002/0183858 relates to tissue scaffold implant devices useful in the repair and/or regeneration of diseased and/or damaged musculoskeletal tissue and that include a foam tissue scaffold component fixedly attached to a scaffold fixation component via partial encapsulation of the fixation component by the foam scaffold component, and to methods of making such tissue scaffold implant devices. The citation does not disclose or suggest the invention defined in present claims.

US 2003/0114936 discloses composite implantable devices having a gradient of one or more of materials, macro-architecture, micro-architecture, or mechanical properties by three-dimensional printing. In preferred embodiments, the implants include complex three-dimensional structures such as creating a gradient of porosities suited for different types of tissue, for example for ingrowth of bone and cartilage in different regions. The citation does not disclose maximising leaching at the surface while minimising it in the interior and so the present claims must be acknowledged as novel and inventive over this citation.

Derwent Abstract 2003-607789/57 discloses a hybrid resin material suitable for making artificial organs having a soluble substance filled in pores or gaps. The soluble substance can be dissolved by a polar solvent to leave pores or gaps in the resin material. The citation does not disclose or suggest the present claims.

All claims meet the criterion of being industrially applicable.

The Claims:

1. A scaffold for at least one of: tissue regeneration and bone growth; the scaffold being fabricated from at least two polymers; a first polymer of the at least two polymers being able to be leached by a solvent, and all other polymers of the at least two polymers being selected from the group consisting of: inert to the solvent, and having a lower dissolution rate in the solvent, wherein leaching of the first polymer is controlled so that leaching is maximized at a surface of the scaffold, and minimized at a core of the scaffold.

2. The scaffold according to claim 1, wherein the polymers are of differing rates of bio-degradability.

3. A scaffold according to claim 1 or 2, wherein the scaffold has a graded porosity with high porosity at a surface of the scaffold, and low porosity at a core of the scaffold.

4. A scaffold as claimed in any one of the preceding claims, wherein the at least two polymers are selected from the group consisting of: natural polymers, a blend of natural polymers and synthetic polymers, synthetic polymers, polyglycolide, polylactide, poly L-lactide, poly DL-lactide, polylactide co-glycolide, poly-€- caprolactone, and polyhydroxybutrate.

5. A scaffold as claimed in any one of the preceding claims, wherein the solvent is selected from the group consisting of: organic solvent, and inorganic solvent.

6. A scaffold as claimed in claim 5, wherein the organic solvent is selected from the group consisting of: acetone, dichloromethane, hex-fluoroisopropanol, chloroform, and alcohol.

7. A scaffold as claimed in any one of the preceding claims, wherein there are two polymers in a ratio in the range 60:40 to 30:70.

8. A method of fabrication of a scaffold for at least one of: tissue regeneration and bone growth; the method comprising:
   (a) blending at least two polymers to form a polymer blend;
   (b) forming the scaffold from the polymer blend;
   (c) leaching the scaffold using a solvent to remove a first polymer of the at least two polymers, all other polymers of the at least two polymers being inert to the solvent,

wherein leaching of the first polymer is controlled so that leaching is maximized at a surface of the scaffold, and minimized at a core of the scaffold.

9. A method as claimed in claim 8, wherein all polymers of the at least two polymers all have a different rate of biodegradability.

10. A method as claimed in claim 8 or 9, wherein there are two polymers in a ratio in the range 60:40 to 30:70.

11. A method as claimed in any one of claims 8 to 10, wherein the at least two polymers are selected from the group consisting of: natural polymers, a blend of natural polymers and synthetic polymers, synthetic polymers, polyglycolide, polylactide, poly L-lactide, poly DL-lactide, polylactide co-glycolide, poly caprolactone, and polyhydroxybutrate.

12. A method as claimed in any one of claims 8 to 11, wherein the solvent is selected from the group consisting of: acetone, dichloromethane, hexfluoroisopropanol, chloroform, and alcohol.

13. A method as claimed in any one of claims 8 to 12, wherein the forming is by at least one method selected from the group consisting of: compression moulding, injection molding, rapid prototyping, and three dimensional printing.

14. A method as claimed in claim 13, wherein compression moulding is at a pressure in the range 0 to 20 Mpa, and at a temperature in the range 25°C to 80°C.

15. A method as claimed in claim 9, wherein the first polymer has a faster rate of bio-degradability.

16. A method as claimed in any one of claims 8 to 15, wherein leaching is in an ultrasonic bath of the solvent.

17. A method as claimed in claim 16, wherein the solvent is at a temperature in the range 25°C to 50°C, frequencies being in the range 1KHz to 40KHz, and exposure time being in the range 5 minutes to 120 minutes.

18. A method as claimed in any one of claims 8 to 16, wherein the at least two polymers are milled prior to blending, milling and blending being in a cryogenic mill to form a particle size in the range 20 to 500µm.

19. A method as claimed in claim 18, wherein the milling is at a cycle dependant upon at least one of: the type of the at least two polymers, and a desired particle size of the at least two polymers.

20. A method as claimed in claim 18 or 19, wherein milling is at a frequency in the range 15 to 30 cycles of one minute each.

21. A method as claimed in any one of claims 18 to 20, wherein during milling, an impaction rate is 15 impacts/second.

22. A method as claimed in any one of claims 8 to 21, wherein the scaffold has a graded porosity with a high porosity at a surface of the scaffold, and a low porosity at a core of the scaffold.

23. A method as claimed in any one of claims 8 to 22, wherein leaching includes: removal, and dissolution.

24. A scaffold when fabricated by the method of any one of claims 8 to 23.

25. A scaffold as claimed in any one of claims 1 to 7, or claim 24, wherein leaching includes: removal, and dissolution.